# GNR: Spirochetes

## Introduction

Spirochetes are Gram-negative bacteria that take the shape of a spiral. In most of Microbiology, we have explored a bacterium, its features, and the diseases it causes. In this lesson, we are going to explore three diseases in detail, then simply say the name of the bacterium that causes it. There will not be the familiar pattern of physiology/virulence/epidemiology/etc. you've come to recognize. Rather than spending a lot of time on the organisms themselves, other than to say they are **Gram-negative spirochetes** that are **really hard to culture** and **really hard to see on Gram stain**, we're going to focus on the diseases they cause.

*Treponema pallidum* causes **syphilis**. *Borrelia burgdorferi* causes **Lyme disease**. *Leptospira interrogans* causes **leptospirosis**.

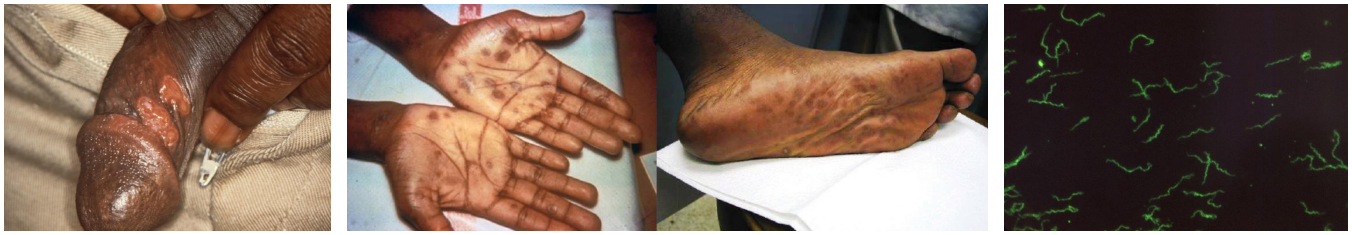
Well . . . you may be asking, "if they are hard to Gram stain, are they Gram negative?" Yes. They have an outer plasma membrane and lipopolysaccharide (LPS, endotoxin). That physiology approximates the Gram-negative organisms more than any other class we will study. Remember that the Gram stain itself is just a scientific procedure so we can see an organism. Being Gram-negative has implications on the structure and function of the bacterial envelope.

There is a theme to spirochetes—difficult to visualize, difficult to culture, but easy to treat. Penicillin G and doxycycline are the drugs of choice to treat all spirochetes. Ceftriaxone can be used as well, but you will see it mentioned only for Lyme disease, and it must be Lyme disease of the CSF.

## *Treponema pallidum* ("Syphilis")

The disease syphilis and the bacterium *Treponema pallidum* are one and the same. We will flip back and forth between the terms syphilis and *Treponema*, using them almost interchangeably. Syphilis cannot survive outside of a human host, so must be transmitted by direct contact. Syphilis is a sexually transmitted infection. The main emphasis is on recognizing the different stages of syphilis and their presentations—primary, secondary, tertiary, and latent. We close with a discussion on pregnancy and syphilis and the Jarisch-Herxheimer reaction.

**Primary syphilis.** Syphilis is a sexually transmitted disease. Ten to 90 days post-exposure, patients will develop a single **nontender ulcer** with a **clean indurated edge**. This ulcer, called a chancre, appears at the site of infection. Inevitably this is tested against other genital lesions that cause ulcers. Syphilis presents with **painless ulcer** with **painful inguinal lymphadenopathy**. Because this is an infection local to the site of contact, at the chancre only, the body has not had time to react to it, so most often **serologic tests are negative** and should not be used to diagnose syphilis. If a vignette provides you with positive nontreponemal antibodies, accept that as evidence of syphilitic infection but do not choose serologic testing to make the diagnosis. You cannot see *Treponema* on Gram stain and you cannot culture it. You can, however, visualize the spirochetes using **immunofluorescent microscopy** (darkfield microscopy, formerly the gold standard, is no longer used, though it may still be the answer on your test). Immunofluorescence uses manufactured antibodies against *Treponema* to visualize *Treponema* in the primary stage. The assay glows when *Treponema* is present. Immunofluorescence is performed on a sample taken from the chancre. Treat primary syphilis with a **single dose of benzathine penicillin**. If penicillin-allergic, the alternative to penicillin is **doxycycline**. Even if not treated, these lesions will heal, giving the patient a false sense of relief. The lymphadenopathy was a sign of the spirochete's ascent from the infection site up the lymphatics. As the lesion heals, the spirochete is in the blood. Not treating with antibiotics allows progression to secondary syphilis.



(a) (b) (c)

**Figure 11.1: Syphilis**
(a) Primary chancre. The lesion is ulcerated, with a clean margin. It is also painless. (b) Secondary syphilis. Very few diseases cause a rash on the palms and soles. Not depicted is the diffuse mucocutaneous copper-colored rash. (c) Immunofluorescent antibodies reveal the spiral-shaped organisms.

**Secondary syphilis.** Months after the initial chancre has healed, the patient will experience a diffuse **mucocutaneous copper-colored rash** of the entirety of the body, including the mouth, and that also **includes hands and soles**. Only three infectious rashes involve the palms and soles (hand-foot-mouth disease caused by Coxsackie A virus, Rocky Mountain spotted fever caused by *Rickettsia rickettsii*, and syphilitic). No other infectious etiology presents simultaneously with a total-body rash and palms and soles, which means that the finding is pathognomonic for secondary syphilis. These lesions are **infectious**, and mucocutaneous contact will transmit syphilis. At this stage, the body has identified the organism, and antibodies will be positive. Antibodies would have been positive at the time the chancre healed; there was just no reason to check for them. The **NONtreponemal antibodies** (VDRL, RPR) are a screening tool and are the first step. The VDRL was formerly used, but with false positives for other diseases (such as lupus), the Rapid Plasma Reagin (the **RPR**) is now used more commonly. The RPR is reported as a dilutional ratio—the larger the number after the colon, the more reactive it is. The RPR will remain positive after treatment, but in low concentrations (reporting a value of 1:2 means the signal was no longer detected at a number of dilutions that is $2^1$, or two dilutions, which to you should be interpreted as "not reactive"), whereas someone actively infected will be in high concentration of antibody (reporting 1:1,024 means it was still positive after 10 dilutions, $2^{10}$, which means very reactive). The problem with nontreponemal antibodies is, as the name implies, they are not specific for syphilis. The **Fluorescent Treponemal Antibody Absorption** (**FTA-ABS**) is the most commonly used **confirmatory test**. It will remain positive for life, even after treatment, and will be positive for any *Treponema* species infection (including Lyme disease). Treatment is with a **single dose of long-acting intramuscular benzathine penicillin G**. Doxycycline is an alternative if penicillin-allergic. The treatment for secondary syphilis is the same treatment as for primary syphilis.

**Latent syphilis.** Latent syphilis is in-between-stages-syphilis. There are two latent syphilis types. Early latent syphilis is the time between the ulcer and the rash. Late latent is after the rash or if the patient doesn't remember the ulcer or rash. The patient survived secondary syphilis (this is easy to do), and didn't get treated (the total-body rash should have prompted a doctor's visit, but it goes away on its own without treatment). Right now, the person in front of you has no symptoms. They don't even remember ever having had the ulcer. But right now in front of you they have positive serology. **Positive serology and no symptoms** is the definition of **latent syphilis**. The only reason you would know whether antibodies were positive is if you went looking. Because they have no symptoms, you wouldn't normally go looking. So, latent syphilis patients are diagnosed because either they screen positive on a nontreponemal screening antibody test obtained for some other diagnosis or because they acquire a condition in which diagnosing syphilis is crucial (new diagnosis of HIV or pregnancy). Early latent syphilis is treated with a single dose of penicillin, or doxycycline could be used as an alternative (the same as for primary and secondary syphilis). Late latent syphilis is treated with **penicillin G**, just given **three times** once every week (q7d × 3 doses).

**Tertiary syphilis.** Leave syphilis in a patient long enough, and it gets everywhere. It invades the walls of the aorta, the spinal cord, the brain . . . everywhere. The immune system fights syphilis with granulomas referred to as **syphilitic gummas**, identified on histology on biopsy specimens. **Syphilitic aortitis** causes aortic dissection as the gummas invade the wall of the small arteries (the vasa vasorum, Cardiology Structure #2: *Aorta Pathology)* compromising the blood supply to the aorta's outer elastic lamina. Syphilitic aortitis causes aortic dissection. **Tabes dorsalis** is the loss of the dorsal column–medial lemniscus tract of the spinal cord, resulting in the loss of proprioception and sensation in the distal extremities. Patients are unable to find their footing and bang their feet into things. Neurocognitive defects, including strange behavior and syphilis "dementia" (neurocognition—can be partially restored with treatment, so it really isn't dementia), occur from brain involvement. The **Argyll-Robertson pupil**, caused by midbrain lesions, permits **accommodation** (pupil contracts when changing focus from distant to near) but prevents the **pupillary light reflex** (pupil does not contract when exposed to light). Antibodies in serum (**serology**) may be **negative** in tertiary syphilis. However, **CSF antibodies will be positive**. Tertiary syphilis is treated with **two weeks' worth of continuous intravenous penicillin**. All neurosyphilis is treated with penicillin, even if the patient is penicillin-allergic.

| PHASE | SYMPTOMS | DIAGNOSTIC TOOLS | SERUM ANTIBODIES | TREATMENT |
|---|---|---|---|---|
| Primary syphilis | Painless ulcer with lymphadenopathy | Darkfield micro<br>Immunofluorescence | Not positive | Penicillin G × 1 |
| Secondary syphilis | Mucocutaneous rash, whole body, includes palms and soles | Non-*Treponema* Ab<br>FTA-Abs | Positive | Penicillin G × 1 |
| Early latent syphilis | Chancre passed, rash hasn't happened | Non-*Treponema* Ab<br>FTA-Abs | Positive | Penicillin G × 1 |
| Late latent syphilis | Asx, no recollection of sxs, antibodies happen to be positive | Non-*Treponema* Ab<br>FTA-Abs | Positive | Penicillin G qWK × 3 |
| Tertiary syphilis | Loss of proprioception, aortitis/aortic dissection, Argyll-Robertson pupil | CSF non-*Trep* ab<br>CSF FTA-Abs | Not positive | Penicillin q4h × 14 days |
| Pregnant syphilis | Any pregnancy gets screened | Non-*Treponema* Ab<br>FTA-Abs | Positive if ever infected | Penicillin G × 1 |

**Table 11.1: Syphilis by Stage**
Presentation, diagnostic tools, treatment.

**Pregnant syphilis.** If mom gets infected with syphilis while pregnant, she will have all the symptoms of an unpregnant woman who gets syphilis. Her treatment is **penicillin**. If she is penicillin-allergic, a decision has to be made. Treatment prevents congenital syphilis. Congenital syphilis is possible only when there is a syphilis-emia (bacteremia). The two times of highest risk are the two times there is syphilis-emia—during the initial infection (primary syphilis) and during secondary syphilis. Any latent syphilis infections can infect baby and cause congenital syphilis, but the risk is low. If a patient can receive penicillin and there is no risk to the mother, treating any diagnosis of syphilis is obvious, eliminating any risk of congenital syphilis. But if mom is penicillin-allergic, we have an issue. The alternative to penicillin is doxycycline. **Doxycycline is contraindicated** in pregnancy, causing bone growth abnormalities. Giving penicillin to a penicillin-allergic patient could result in anaphylaxis. Not giving penicillin risks congenital syphilis. Therefore, we use risk/benefit analysis. If primary or secondary syphilis, where the likelihood of

congenital syphilis is high, we perform **penicillin desensitization**, admitting her to the hospital, giving her incremental amounts of penicillin. If she is in latent syphilis, where the likelihood of congenital syphilis is low, we **defer treatment** until after delivery, then use doxycycline.

Active syphilis-emia infection early in the pregnancy results in a dead baby. Active syphilis-emia infection later in the pregnancy results in congenital syphilis—**saddle nose** (sunken appearance), **Hutchinson teeth** (central notch in each tooth), and **mulberry molars** (molars have too many cusps). Alternatives to penicillin, such as doxycycline, are contraindicated in pregnancy. To save baby, mom gets penicillin, even if penicillin-allergic.

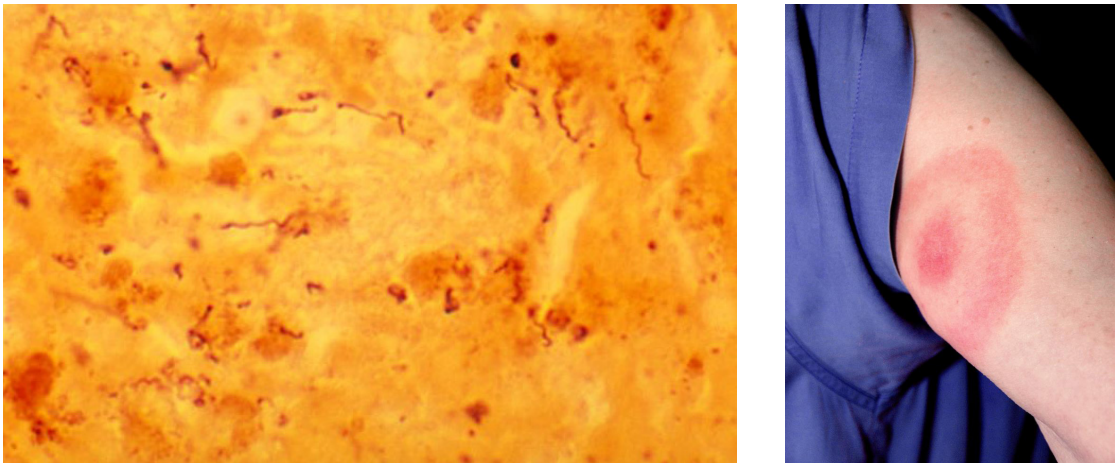
| PREGNANT STATUS | PENICILLIN ALLERGY | SYPHILIS | TREATMENT |
|---|---|---|---|
| Pregnant | Penicillin-allergic | Primary or secondary | Penicillin desensitization |
| Pregnant | Penicillin-allergic | Latent syphilis | Defer, use doxycycline after |
| Pregnant | Not allergic | Irrelevant | Penicillin |
| Not pregnant | Penicillin-allergic | Not tertiary | Doxycycline |
| Not pregnant | Not allergic | Irrelevant | Penicillin |

**Table 11.2: Treatment of Syphilis**

**Jarisch-Herxheimer reaction.** As the spirochete dies, lipo-poly-saccharide (LPS, endotoxin) is released, inducing a severe inflammatory reaction. Within 24 hours of antibiotics administration, **fever, rigors, leukopenia,** and a **diffuse macular rash** may occur. This reaction rarely happens, but is also not unanticipated. The risk is highest during disseminated infection during secondary syphilis. It is possible in any spirochete infection, but you should associate this reaction with syphilis. It is a sign of bacterial death and not a penicillin allergy.

## *Borrelia burgdorferi* ("Lyme Disease")

Lyme disease is caused by the spirochete *Borrelia burgdorferi*. The spirochete is carried by the ***Ixodes* tick.** The tick vector is housed in animals. The larval and **nymph** stages of *Ixodes*' development is on **white-footed mice.** The adult stage of *Ixodes*' life cycle is on **white-tailed deer**. The nymph form of the tick is tiny, and is the form that causes 90% of human disease. The tick the patient notices and removes from their skin is unlikely to be the tick that transmits Lyme disease. The recollection (or lack thereof) of tick sightings or tick removal is irrelevant to the clinical reasoning. Exposure, simply by being where ticks are, is enough. The tick is carried on its mammal host into the woods, where it is left behind. Humans happen upon said tick. The tick bites the human. *Borrelia,* who just happens to be hanging out in the *Ixodes* tick, is then injected into skin. The white-footed mice and the white-tailed deer need not be present for the infection. Lyme disease is the **most common vector-borne disease** in the US. The organisms that carry the vectors are found in regionally distinct locations. Most famous is the northeastern United States, particularly in a region of **Connecticut** with neighboring towns involving the word Lyme (Old Lyme, Lyme, East Lyme), from which the disease gets its name. Other regional areas throughout the country include mountainous California and northern Midwest. The point is, "you don't have to be in Lyme, Connecticut to get Lyme disease, but you do need to be outdoors and get bitten by a tick." However, on an exam, because Lyme disease's highest prevalence is in the northeastern United States, the exam must tell you woodland exposure in New England.



(a) (b)

**Figure 11.2: Lyme Disease**
(a) Spirochete visible on blood smear, usually not seen because with Lyme disease the number of organisms is too small to catch one in a blood sample. (b) Erythema migrans. This particular version has a central redness, a zone of clear skin, then another zone of red around the area of clearing.

Lyme disease has three phases—early Lyme, invasive Lyme, and Lyme arthritis.

**Phase 1: Early Lyme.** The patient was bit by a deer tick. Deer ticks are amazingly small. The patient had no idea they were bit by a tick. But sometime in the past month (incubation period 3–30 days) they went hiking. Now they have a **flu-like syndrome** (fever, myalgias, and malaise) and a rash. The rash is called **erythema chronicum migrans**. It starts as a **red rash** (erythema) that is flat and round. Over a long time, over the next month (chronicum) the red rash spreads outward (migrates), leaving normal, non-red skin where the rash was. This center of normal skin, a ring of red skin migrating out, then normal skin again, gives it a **targetoid** or **bull's-eye-shaped appearance.** (the true rash may leave a red spot in the center of the normal skin, be all red, or any permutation; you should just learn "targetoid"). At this point, a confirmative diagnosis is not even needed, and presumptive treatment with **doxycycline** is started. If diagnosis is warranted, **serum antibodies** can show that they were at some point infected. The problem here is that antibodies are positive for any spirochetes, never turn negative, and aren't actually confirming a current *Borrelia* infection. The exposure and the rash are enough to treat with doxycycline.

**Phase 2: Invasive Lyme.** The targetoid rash improves, but the fevers and myalgias don't. It has been about two months since the hike and the patient has endured the symptoms of phase 1 for about one month. The spirochete is no longer local in the skin where the bite was, but has gained access to the bloodstream. As it disseminates, it gets into all sorts of tissues. There will be **more fevers** and now **swollen lymphadenopathy**. Nerve findings include **Bell's palsy**, and severe forms can cause a **subacute meningitis** (means not-that-bad-but-still-meningitis). Dissemination to the heart results in **bradyarrhythmias** and **AV dissociation** (heart block). At this point, serology is helpful, but still with the caution issued above. If they have never been treated for Lyme, they should now receive **IV ceftriaxone**, the therapy of choice for invasive Lyme.

**Phase 3: Late Lyme.** Late Lyme, also called Lyme arthritis, presents with impressive effusions. Arthrocentesis shows inflammatory arthritis (not infectious arthritis) levels of white blood cells. While *Borrelia burgdorferi* is never cultured, DNA from the bacteria is found in synovial fluid, confirmed by PCR. The diagnosis can also be made on **plasma serologies**. If never treated for Lyme, **IV ceftriaxone** for four weeks eradicates the bug. If inflammation happens after IV therapy—which will eradicate

the infection—NSAIDs and DMARDs can be used for the arthritis. **Do not repeat long-term IV antibiotic therapy.**

**Phase *Non Existat*: Chronic Lyme.** Is chronic Lyme a real thing? Patients who were infected with Lyme often complain of long-lasting arthralgias. Long-lasting pain is very real. It is the cause of that long-lasting pain that we have trouble with. Chronic Lyme is treated with long-term antibiotics. If that were going to work, the bacteria would be dead and the symptoms would abate. But patients with chronic Lyme treated with long-term antibiotics don't improve their symptoms. If the cause is antigenic mimicry, antibiotics won't help. In almost every case there are psychosocial factors that could provide an alternative explanation to very real psychosomatic pain. The presence of antibody to Lyme disease does not mean an active infection. To an untrained lay person, ongoing positive antibodies are a sign of ongoing infection. With popular and wealthy people popularizing the idea of chronic Lyme as a diagnosis, physicians will be asked to deal with these sorts of issues. Medical microbiology texts do not address chronic Lyme. We do. If you have a patient with "chronic Lyme" or "Lyme disease-induced arthritis" distant from the infection and after antibiotics, look for something else. The arthritis, the pain, the symptoms are real. The cause is not *Borrelia burgdorferi* nor the antibodies to *Borrelia burgdorferi*.

We do not have the space to reproduce it here, but the IDSA says so, too. Check out page 19. https://www.idsociety.org/globalassets/idsa/topics-of-interest/lyme/idsalymediseasefinalreport.pdf

There are over-the-counter serologic assays that allow lay people to assess for antibodies to fungus, bacteria, and viruses. They are marketed as a means of determining whether they or their loved ones are infected. Antibodies means exposure only. In many cases, it also means immunity.

| PHASE | TIMELINE | SYMPTOMS | TREATMENT |
|---|---|---|---|
| 1—Early Lyme | Exposure to *Ixodes* tick one week prior | Erythema migrans, targetoid lesion, arthralgias, fever | Doxycycline oral |
| 2—Invasive Lyme | Exposure to *Ixodes* tick two weeks prior | Neurologic—Bell's palsy<br>Cardiac—Heart block<br>Migratory arthralgias | Ceftriaxone IV |
| 3—Late Lyme | Any amount of time after phase 2 without treatment | Arthritis, effusions, DNA positive synovial effusions | Ceftriaxone IV |
| *Non Existat*—Chronic Lyme | Any time after adequate antibiotic treatment | Arthralgias, limited effusions | NSAIDs, DMARDs, psychotherapy |

**Table 11.3: Lyme Disease**

## *Leptospira interrogans* ("Who?")

*Leptospira* is a low-yield organism, especially in comparison to syphilis and Lyme, but it rounds off our medically important spirochetes. It is a **Gram-negative spirochete** that winds up into a tight **coil**, with hooks on one or both of its ends. *Leptospira interrogans* causes disease in **humans**. Leptospira lives in **animals**, within the renal tubules specifically, and is shed in large number in the **urine of animals**—dogs, rats, livestock. Recreational water exposure—lakes, ponds—or occupational exposure to animals and soil—livestock farmers—is how humans become infected. *Leptospira* penetrates mucosal membranes and even broken skin. There are two phases—leptospiremia and immune.

The **leptospiremic phase** (phase 1) is caused by the bacteria invading the bloodstream and CSF. Leptospiremic bacteria are Gram-negative and have an outer membrane with LPS. Bacteremia therefore causes high-spiking fevers, malaise, headaches, and myalgias—nonspecific findings that could represent any infection. The patient feels awful, but there is nothing to tip off a clinician that this is anything other than a viral illness. If a blood smear were done, *Leptospira* would be seen in the blood. If CSF were drawn, *Leptospira* would be seen in CSF. But no one looks, because there is not a strong indication to look. Knowledge of recent use of jet skis or summer holidays may prompt consideration, but leptospirosis is not something commonly considered in clinical practice.

The symptoms may remit or the progress to the **immune phase** (phase 2). Now symptoms are not a product of the spirochete, but rather of the immune response against it. The formation of **IgM antibodies** causes rapid identification and killing of the organism. However, it has already disseminated, so whatever organ it is in will suffer inflammatory damage as the immune system clears the infection. If the spirochete gets into the brain, rapid inflammation results in **meningeal signs** (photophobia, stiff neck, fever, headache), and the CSF will show an "aseptic meningitis." Because the course is often indolent, even severe presentations of leptospirosis meningitis go undetected—the lumbar puncture does not show bacterial meningitis, and the diagnosis is self-resolving aseptic meningitis. If the spirochete gets into the liver, the immune phase kills the spirochete by killing the liver (icteric disease, **Weil's disease,** fulminant hepatic failure in 10% of Weil's disease), resulting in **jaundice and an elevation of liver function tests**. This may be fatal. If the spirochete gets into the kidney (it lives in the renal tubules of animals; we humans are also animals who have renal tubules), the immune phase results in renal failure. Those who survive show no permanent damage to the liver or the kidneys.

Leptospirosis is usually not fatal, particularly in the absence of icteric disease. Patients with a confirmed diagnosis—PCR of the urine is the easiest test to collect and most reliable—should be treated with **intravenous doxycycline** or **intravenous penicillin**.